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Stroke and antiphospholipid syndrome—antiphospholipid antibodies are a risk factor for an ischemic cerebrovascular event

Nataša Gašperšič[1] · Marjan Zaletel[2] · Jan Kobal[2] · Polona Žigon[1] · Saša Čučnik[1,3] · Snežna Sodin Šemrl[1,4] ·
Matija Tomšič[1,5] · Aleš Ambrožič[1]

Abstract

Testing for antiphospholipid antibodies could be an important part in determining the cause of a cerebrovascular event (CVE). Currently, it is also unknown whether antiphospholipid antibodies represent a risk factor for the development of a CVE and whether the selected therapy options are efficacious. So, this study aimed at (1) determining the frequency of patients experiencing a CVE and fulfilling the laboratory criterion for an antiphospholipid syndrome (APS), (2) investigating whether the persistent presence of antiphospholipid antibodies represented a risk factor for a CVE, and (3) focusing on the efficacy of the selected treatment strategy in the first year after the CVE. Eighty-nine patients with an acute CVE were prospectively followed for 1 year. At least two sera from each were tested for lupus anticoagulants, anticardiolipin, anti-β2-glycoprotein I, anti-phosphatidylserine/ prothrombin and anti-annexin V antibodies. Twenty out of eighty-nine (22%) of CVE patients fulfilled the criteria for APS (17/20 for definitive and 3 for probable APS). There was a significant association between persistently present antiphospholipid antibodies and the CVE (OR, 4.62). No statistically significant difference was found in the CVE recurrence rate between APS-CVE and non-APS-CVE patients being treated mainly with acetyl salicylic acid. Antiphospholipid antibodies represent an independent risk factor for a CVE. In the first year after the CVE, antiplatelet therapy seemed to be sufficient in secondary CVE thromboprophylaxis in most APS patients.

Keywords Antiphospholipid antibody · Risk · Stroke · Treatment

Rheumatology in Slovenia: Clinical practice and translational research

✉ Nataša Gašperšič
natasa.gaspersic@kclj.si

1 Department of Rheumatology, University Medical Centre Ljubljana, Vodnikova 62, SI-1000 Ljubljana, Slovenia

2 Department of Neurology, University Medical Centre Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia

3 Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, SI-1000 Ljubljana, Slovenia

4 Faculty of Mathematics, Natural Sciences and Information Technologies, University of Primorska, Glagoljaška 8, SI-6000 Koper, Slovenia

5 Faculty of Medicine, University of Ljubljana, Vrazov trg 2, SI-1104 Ljubljana, Slovenia

Introduction

Ischemic cerebrovascular events (CVE) are frequent in patients with underlying vascular risk factors, such as arterial hypertension, hyperlipidemia, diabetes, smoking, and obesity. Nevertheless, in a large proportion of patients, especially younger adults with a CVE, the cause often remains unexplained. In such cases, a more extensive search is mandatory, with an emphasis on structural cardiac or vessel disease, autoimmune diseases, and hypercoagulable states. One among the acquired thrombophilia is an autoimmune disorder, antiphospholipid syndrome (APS), a multi-organ disease, which can also affect the central nervous system, with a stroke, and a transient ischemic attack (TIA) being the most common neurological manifestations [1, 2].

The classification criteria considered "definite APS" is a condition in which at least one of the two major clinical manifestations (i.e., thrombosis or pregnancy morbidity) is met and one of three standardized laboratory assays to detect antiphospholipid antibodies (aPL) is positive, specifically

IgG/M anticardiolipin (aCL), anti-β2-glycoprotein I antibodies (aβ2GPI), or lupus anticoagulant (LA) [3]. However, several other autoantibodies, directed at other negatively charged phospholipids and their complexes with protein cofactors, have been proposed to be relevant to APS [4]. Among them are anti-phosphatidylserine/prothrombin (aPS/PT) and anti-annexin V antibodies (aANXV) [5, 6], as well as IgA aCL and IgA aβ2GPI. Such "non-criteria" aPL have not yet been included in the classification criteria of APS, however, they contribute to a "probable APS" [7].

The aim of our study was therefore primarily to determine the frequency of patients experiencing CVE and fulfilling the classification criteria for APS [3] or probable APS. Additionally, we focused on whether the persistent presence of aPL represents a risk factor for experiencing an episode of a CVE. We also aimed at defining the optimal treatment strategy in the first year after a CVE.

Materials and methods

The study was performed as a single-center, prospective follow-up clinical trial. Patients younger than 69 years who had experienced an acute CVE (first or recurrent) were consecutively included. Patients with a known active or newly diagnosed malignant disease were excluded. Eighty-nine patients (male/female, 67/22; mean age, 48 years, ranging from 18 to 67 years) with a CVE were enrolled. They were all followed for 1 year starting immediately after they had been diagnosed by the neurologist at the Department of Neurology, University Medical Centre Ljubljana (UMC-LJ), Slovenia. The diagnoses, based on patient history, clinical manifestations, and an objective verification using computer tomography (CT), magnetic resonance images (MRI), and/or angiography, were set during admission. In the comparative group, patients with other central nervous system diseases were included, namely patients with migraine and Huntington's disease, all in the chronic phase of their disease. We enrolled 25 patients with migraine without complications (male/female, 5/20; mean age, 40 years, ranging from 18 to 58 years) and 20 patients with Huntington's disease (male/female, 8/12; mean age, 53 years, ranging from 32 to 67 years). All patients signed an informed consent form before enrolment in the study. The study was conducted within the National Research Programme "Systemic autoimmune diseases" #P3-0314 (funded by the Slovenian Research Agency), with ethical approval #163/02/09, approved by the Slovene National Medical Ethics Committee.

Demographic data on smoking, hypertension, diabetes, the use of oral contraceptives, and an evaluation for additional autoimmune diseases were obtained through the following visits at 3, 6 and 12 months after the CVE and for the comparative patients twice, 3 months apart at the Department of Rheumatology, UMC-LJ. Patients reporting daily smoking at least until the index event were defined as smokers; occasional smokers were classified as non-smokers. Hypertension was defined as a systolic blood pressure of ≥ 160 mmHg, and/or diastolic blood pressure of ≥ 95 mmHg, and/or the use of an antihypertensive medication. Hypercholesterolemia was defined when the serum cholesterol exceeded 5.2 mmol/l at the index event and/or the use of an antihyperlipidemia medication. Blood samples were collected at the index event, 3, 6, and 12 months after the CVE and twice, 3 months apart, for the check-ups. Aliquots of sera were immediately frozen and stored at − 80 °C until analyzed.

Immunoserological testing was performed for different aPL. For LA determination, plasma samples were analyzed according to the guidelines [8] using a coagulation analyzer (BCS Siemens) and reagents (Siemens AG, Munich, Germany) following the manufacturer's instructions. IgG/IgM/IgA aCL and aβ2GPI were determined by an *in-house* ELISAs [9, 10]. IgG/IgM anti-phosphatidylserine/prothrombin (aPS/PT) antibodies were determined with an *in-house* aPS/PT ELISA [11] and IgG/IgM aANXV were measured using an ELISA from Orgentec Diagnostika GmbH, Mainz, Germany, according to the manufacturer's instructions. The cut-off for all *in-house* ELISAs was set at the 99th percentile of 220 healthy blood donors.

Patients with a persistent presence (on two or more occasions, at least 12 weeks apart, and for CVE patients 3 months after the CVE) of at least one type of the tested criteria aPL were considered as definite APS. Patients with a persistent presence of other aPL, not included in the APS classification criteria [3], were considered as probable APS.

Statistical analyses were performed using the SPSS 15.0 program. For testing the differences between the CVE and the comparative group, chi-square and Mann-Whitney U tests were performed. A 2-sided probability (p) value of less than 0.05 was considered statistically significant. The multiple logistic regression model was used to test the influence of different risk factors on CVE occurrence. The results were approximated by the odds ratio with its 95% confidence interval (OR [95%]).

Results

Patients' characteristics

The demographic and clinical characteristics of the patients enrolled are shown in Table 1. We found six patients with an additional autoimmune disease, namely three CVE patients with the disease already identified and treated at the time of the CVE diagnosis (one rheumatoid arthritis, one IgA nephropathy, and one psoriatic arthritis), with the latter patient subsequently fulfilling the classification APS criteria, and

Table 1 Patients' demographic and clinical characteristics

	CVE patients ($n = 89$)	Non-CVE patients ($n = 45$)			p value (CVE vs. non-CVE)
		Total	Migraine ($n = 25$)	Huntington's disease ($n = 20$)	
Sex (M:F)	67:22	13:32	5:20	8:12	< 0.01*
Age at inclusion (years ± SD)	47.5 ± 9.8	45.4 ± 12.1	39.6 ± 11.5	52.7.6 ± 8.6	0.395
Younger than 50 years	53 (60%)	28 (62%)	19	9	0.852
Smoking	56 (63%)	9 (20%)	2	7	< 0.01*
Arterial hypertension	49 (55%)	5 (11%)	3	2	< 0.01*
Hyperlipidemia	58 (65%)	3 (7%)	0	3	< 0.01*
Diabetes mellitus	13 (15%)	1 (2%)	0	1	0.034*
Other AI disease	3 (3%)	3 (7%)	3	0	0.105

CVE cerebrovascular event, *M* male, *F* female, *AI* autoimmune, *statistically significant *p* value < 0.05

three migraine patients (one with rheumatoid arthritis and Sjögren syndrome, one with the Sjögren syndrome, and one with peripheral spondyloarthritis), none of which fulfilled the APS laboratory criteria. Patients with Huntington's disease had no additional systemic autoimmune disease. Classical cardiovascular thrombotic risk factors were all statistically significantly more common in the CVE group (Table 1).

Antiphospholipid antibodies and CVE

Among 89 CVE patients, 20 (22%) were positive for a particular tested aPL at least twice, with the first testing no earlier than 3 months after the CVE. In this positive group, 17 had the criteria aPL, while three had only non-criteria aPL (the first aCL IgA, the second aANXV IgG, and the last aβ2GPI IgA together with aPS/PT IgM). Only 4/20 of those APS-CVE patients had simultaneously more than one type of aPL present (three patients had a combination of two criteria and one patient the combination of two non-criteria aPL, while there were no triple or more positive patients).

Considering the age of the patients, there was no statistically significant difference in the frequency of CVE-APS patients in the group of those younger and those older than 50 years. Namely, 10/53 (19%) APS-CVE patients were younger and 10/36 (28%) older than 50 years ($p = 0.44$). Importantly, using the TOAST CVE classification [12] with persistently detected aPL, the cause of the CVE could be consecutively explained in 14/89 (16%) of the CVE patients with the formerly unexplained CVE (Fig. 1).

Using a multiple logistic regression model, we found a significant association between hyperlipidemia (OR, 15.23; 95% CI, 4.13–56.15) and arterial hypertension (OR, 4.31; 95% CI, 1.33–13.92), while a significant association was also found between persistently present aPL and the CVE (OR, 4.62; 95% CI, 1.09–19.66).

APS-CVE treatment

Immediately following the CVE, all patients started the treatment with acetyl salicylic acid (together with other medications necessary in secondary stroke prevention according to the guidelines [13]). Anticoagulant therapy was introduced only if so required due to other accompanying diseases or conditions (venous sinus thrombosis, childbirth period, newly confirmed atrial fibrillation, or hereditary thrombophilia). In our study, immediately following the CVE, anticoagulant treatment was indicated in 8/89 (9%) CVE patients, two patients had a CVE and venous sinus thrombosis, two others experienced a CVE in the childbirth period, and in four patients, new atrial fibrillation was confirmed. Later, anticoagulant therapy was introduced in three APS-CVE patients, namely in two patients due to confirmed additional hereditary thrombophilia and in one due to a CVE reoccurrence. All other patients were treated only with acetyl salicylic acid. During this treatment strategy, in the first year of follow-up, we observed no differences in the CVE recurrence frequency between APS-CVE and the non-APS-CVE group (Table 2).

Patients with APS-CVE were divided into two groups, according to the profile of the aPL. We defined them as having a high risk profile, when they were positive at least two times 12 weeks apart for more than one criteria antiphospholipid antibody (LA, aCL IgG/M, aβ2GPI IgG/M) or for LA only (category I and IIa, according to the revised classification criteria [3]). We found 9/20 (45%) APS-CVE patients as having a high-risk profile (six of them with solely LA positivity and no one with triple positivity). The rest 11/20 (55%) patients had a low-risk profile, having a single-criterion antiphospholipid antibody or non-criteria aPL (aCL IgA, aβ2GPI IgA, aPT/PS IgG/M, and/or aANXV IgG/M). In the first year of follow-up, there were 3/11 (27%) patients with a low-risk profile and 1/9 (11%) patients with a high-risk profile aPL, who experienced a CVE recurrence, which was not statistically significantly different ($p = 0.591$).
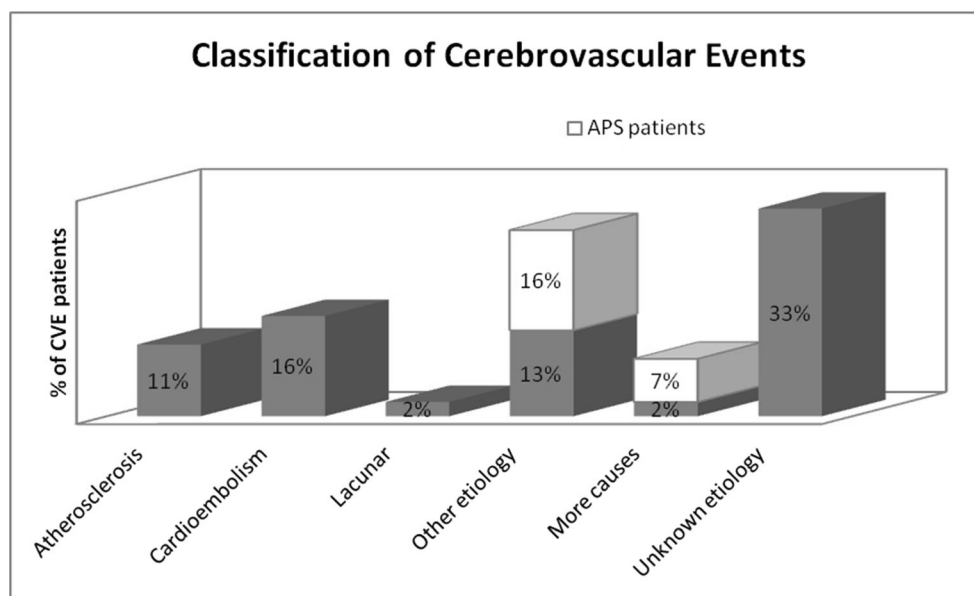
Fig. 1 Classification of cerebrovascular events according to the TOAST classification [9]. APS, antiphospholipid syndrome, definitive and probable; CVE, cerebrovascular event; atherosclerosis, a significant (> 50%) atherosclerotic stenosis or occlusion of the large artery; cardioembolism, an arterial occlusion due to an embolus arising in the heart; lacunar, a small artery occlusion; other etiology, other determined etiology, such as nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorders; more causes, when two or more potential causes of stroke present; unknown etiology, despite evaluation, the stroke cause could not be determined

Discussion

Antiphospholipid antibodies have been recognized as one of the possible etiological factors for a CVE [14]. In the present study, we found aPL in 20/89 (22%) of CVE patients with 3/20 patients having only non-criteria aPL. The detected frequency is somewhat higher than the recent APS ACTION findings that reported 13.5% of ischemic stroke patients having APS [15]. But it should be considered that a direct comparison among different studies is impossible due to the different study protocols: in some, aPL were tested only once, in some older studies, not all the criteria aPL were tested, while in others, similar to our own, non-criteria aPL were also considered. Additionally, none of the methods for the detection of aPL have been standardized, therefore a considerable degree of interlaboratory variation still remains.

While routine testing for aPL is not recommended in all CVE patients, it comes into consideration in patients with suspected APS or in those with no alternative explanation for the ischemic clinical event, such as atherosclerosis, carotid stenosis, or atrial fibrillation [13, 16]. Importantly, in our group of CVE patients, we confirmed APS in 16% (14/89) of formerly considered to be patients with cryptogenic stroke, six patients were younger and eight APS patients older than 50 years. All these patients had persistently present aPL in intervals and levels, as defined by the APS classification criteria [3]. On the other hand, for non-criteria aPL, their persistent elevation had exceeded the value of the 99th percentile of healthy blood donors. Despite the fact that APS is usually considered as a cause of a CVE in younger patients, there are descriptions of disease onset, as well in the elderly [17]. Similarly to our results, APS should be evaluated within cryptogenic CVE patients of all ages, as a cause of CVE.

Understanding the basics of ASP, it has already been stated that aPL are not only a diagnostic marker for APS but also a risk factor for thrombosis and pregnancy complications [18].

Table 2 Treatment strategy after a CVE. Anticoagulant therapy was started in patients with a CVE having accompanying conditions requiring such treatment (venous sinus thrombosis, a CVE in the childbirth period, newly confirmed atrial fibrillation patients or later detected additional hereditary thrombophilia, or in APS patients when a CVE reoccurred). All other patients were treated with acetyl salicylic acid

	APS-CVE ($n = 20$)	Non-APS-CVE ($n = 69$)	p value (APS-CVE vs. non-APS-CVE)
Immediate anticoagulant therapy	2 (10%)	6 (9%)	1.000
Later anticoagulant therapy	3 (15%)	0 (0%)	0.010*
Antiaggregation therapy	15 (75%)	63 (91%)	0.115
CVE reoccurrence	4 (20%)	13 (19%)	1.000

CVE cerebrovascular event, *APS* antiphospholipid syndrome, *statistically significant p value < 0.05

The results of the present study also support the concept that aPL themselves represent an independent risk factor for thrombosis. In accordance with the recent systematic review of Sciascia et al. [15], we similarly found that continuously present aPL increase the risk of a CVE (OR, 4.62).

While a significant association between aPL and CVE is noted, the risk of the recurrence of aPL-associated thrombosis after the first CVE is not well defined [19]. Systematic reviews report that the profile of aPL represents a characteristic risk for further development of APS clinical manifestations. LA were reported to be a stronger risk factor, among the three criteria aPL [20], while some newer data have showed that the risk of thrombosis in solely LA-positive APS patients is low [21]. However, undoubtedly the thrombotic risk increases with the number of positive aPL tests, particularly in patients having all three types of criteria aPL positive (referred to as triple positivity), who are at a higher risk for the occurrence of a thrombotic event [22, 23]. Because of their important causative role in thrombosis, a secondary prevention of further thrombotic events in aPL-positive patients is very important. However, there is a lack of a clear consensus regarding the optimal antithrombotic management of patients with an ischemic stroke/TIA and aPL [18, 24]. The latest AHA/ASA guidelines for the prevention of stroke suggest considering anticoagulant therapy depending on the perception of the risk for recurrent thrombotic events and bleeding in patients with an ischemic stroke or TIA, who meet the criteria for APS. However, in these patients, in whom anticoagulation had not begun, antiplatelet therapy is recommended [13].

In our study, all CVE patients started treatment with acetyl salicylic acid immediately at the time of the CVE, and anticoagulant therapy was introduced only if additional individual patient's characteristics showed a need. Following such a treatment regimen in the first year after a CVE, we found no statistically significant differences between the frequency of a CVE reoccurrence in the APS-CVE and non-APS-CVE groups (Table 2). That may also be due to the fact that the number of APS-CVE patients with two or more types of aPL was rather low (3/20 patients had a combination of two criteria and one patient the combination of two non-criteria aPL, while there were no triple-positive patients). Regarding these results, in the first year after a CVE or at least until APS confirmation, a secondary CVE prevention strategy with the focus on antiplatelet therapy together with the control of other risk factors (e.g., strict control of classical cardiovascular risk factors and thromboprophylaxis with low molecular weight heparin in high-risk situations for thrombosis) seems to be sufficient.

Possible limitations of our study are certainly a relatively small number of patients and only a 1 year systematic follow-up of the CVE patients. However, although the risk of a stroke reoccurrence remains high for several years, it is the highest in the first year after the first CVE [25]. Additionally, according to our clinical experience and considering the results of previous studies [26], as well as the mechanism of drug action [27], it seems reasonable to modulate treatment decisions during a careful follow-up of APS patients. There is a need to fortify the secondary thromboprophylaxis in APS-CVE patients when (1) they experience a new CVE or other vascular thrombotic event, (2) they have a high-risk profile of aPL (especially in triple positivity), or (3) in clinically asymptomatic patients, when new ischemic lesions are seen with a control brain MRI 1 year after the index event, despite regular antiplatelet therapy. In such cases, a treatment strategy with a combination of moderate-intensity warfarin (INR, 2–3) with acetyl salicylic acid should be considered.

In conclusion, persistently present aPL, as required to fulfill the APS criteria, are one of the possible etiologic factors for a CVE. They also seem to increase the risk for a CVE at least fourfold. Therefore, they should be examined, both for determining the cause of the CVE, especially in patients with a CVE of unknown etiology, as well as for providing further optimal treatment decisions.

Compliance with ethical standards

Disclosures None.

Ethics approval The study was approved by the Slovene National Medical Ethics Committee (163/02/09).

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